REMARKS

Consideration and allowance of the subject application are respectfully requested.

Claims 1-20 and 22-45 are pending in the application. Basis for new claims 44 and 45 can be found in original claim 1. Claims 30 and 31 have only been amended to correct a typographical error. No new matter has been added.

Applicants respectfully submit that the Office Action incorrectly refers to an ART 34 AMDT and that claims 1-27 are pending. Applicants respectfully request that the Preliminary Amendment filed as the original filing on January 10, 2002 adding new claims 28-43 and canceling claim 21 be properly entered. The claims shown above take the January 10, 2002 Preliminary Amendment into account.

The rejection of claims 1-4, 7, 10, 11, 13, 15, 22 and 27 under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,858,410 (Muller) is respectfully traversed. The claimed invention is not anticipated by Muller for the following reasons.

Applicants have now found that during homogenization using a piston-gap homogenizer water vapor can be created in the form of bubbles, which subsequently implode. The resulting implosion shock waves lead to particle diminution. However, many materials are destroyed, melted or otherwise undesirably altered by these violent shock waves. See page 3, last paragraph to page 4, first paragraph, in the present translated application.

Applicants have solved these problems by providing a far more gentler method of obtaining the same particle size without using the implosion shock waves by:

1) reducing the temperature of the medium being homogenized; and/or

2) reducing or eleminating the use of water.

Muller does not address these problems. Muller, thus, does not specifically nor implicitly disclose the claimed "temperature under 90°C" or use of an "anhydrous or water reduced medium" to solve these problems. Since Muller does not disclose

these claim elements, the claimed invention cannot be anticipated by Muller for these reasons alone.

Prior to the present invention, it was believed throughout the art that cavitation was the main source of diminution, as a consequence high pressure homogenization was generally described in water. Especially increased effectiveness was claimed when homogenizing at higher temperatures. (See for example, EP-B-0 605 933 of B.W Müller, cited in the present patent application). The reason for the increased efficiency at higher temperatures is the increased vapour pressure of water at higher temperature which provides increased cavitation. Therefore, the general teaching is the need to use water at higher temperatures for increased cavitation formation to provide particle diminution.

Contrary to this teaching, according to the present invention homogenization is performed in media other than water (anhydrous) or water reduced, and/or at lower temperatures to reduce or eliminate cavitation caused by water vapor. Surprisingly, a comparable size diminution can be obtained without using destructive implosion shock waves. Contrary, to the general knowledge in the art, Applicants have found that cavitation is not the dominating diminution principle in the present invention. This is further supported by performing homogenization at lower temperatures, e.g. at 0° Celcius or below. A surprisingly similar efficiency in diminution is observed, which is contrary to the general beliefs in the art.

On page 3 of the Office Action, the Examiner cites col. 3, lines 20-25 of Muller as evidence that microparticles are prepared in viscous media. However, a closer reading of Muller shows that this disclosure does not refer to high pressure homogenization, but rather to the milling techniques mentioned in col. 2, lines 56-60, i.e. colloid mills (rotor stator principle), ball or pearl mills. There is no teaching for using these media for high pressure homogenization with piston-gap or jet stream homogenizers. For this reason alone, claims 10, 13, 15, 22 and 27 are not anticipated by Muller.

The Examiner also cites col. 20, lines 5-10 of Muller. However, this disclosure does not refer to viscous dispersion media, but rather only that the drug is dispersed in a dispersion medium, not specifying the medium. However, reading

this disclosure in connection with the entire text of Muller it is quite clear that it means water, with dissolved surfactants. The Examiner then cites col. 20, lines 35-40 of Muller as evidence that particles have been produced after the insoluble or moderately soluble drugs have been dissolved in organic solvent at room temperature. First of all, after dissolution of a drug, preparation of particles by grinding is not possible any more, because after dissolution a solution is present. Secondly, this disclosure does not describe dissolution or dispersion of a drug in organic solvents. This disclosure only specifies the drugs based on their characteristic, i.e. the characteristic is that the "carrier comprises particles of at least one therapeutic active which is insoluble in water, aqueous media and/or organic solvents." A solubility property is described, being a characteristic of the particles. For this reason alone, claims 10, 13, 15, 22 and 27 are not anticipated by Muller.

The Examiner cites again col. 19, lines 60-65 of Muller as anticipating claims 11 and 13. However, this disclosure only refers to subsequent incorporation of the particles (after production) in another medium, e.g. PEG or glycerides (e.g. in gels or ointments). For this reason alone and for the reasons provided above regarding col. 19, lines 60-65, claims 11 and 13 are not anticipated by Muller.

Since Muller does not disclose all of the claimed elements as discussed above, Muller cannot anticipate the claimed invention. Accordingly, withdrawal of the Section 102 rejection is respectfully requested.

The rejection of claims 1-27 under 35 U.S.C. § 103 as being unpatentable over WO 98/14174 (Desai) is respectfully traversed. The claimed invention is not obvious over Desai for the following reasons.

As discussed above, Applicants have now found that during homgenization using a piston-gap homogenizer, water vapor can be created in the form of bubbles, which subsequently implode. The resulting implosion shock waves lead to particle diminution. However, many materials are destroyed, melted or otherwise undesirably altered by these violent shock waves. See page 3, last paragraph to page 4, first paragraph, in the present translated application.

Applicants have solved these problem by providing a far more gentler method of obtaining the same particle size without using the implosion shock waves:

1) reducing the temperature of the medium being homogenized; and/or

2) reducing or eleminating the use of water.

As discussed above, prior to the present invention, it was believed throughout the art that cavitation is the main source of diminution, as a consequence high pressure homogenization is generally described in water and especially increased effectiveness is claimed when homogenizing at higher temperatures. The reason for the increased efficiency at higher temperatures is the increased vapour pressure of water at higher temperature which provides increased cavitation. Therefore, the general teaching is the need to use water at higher temperatures to provide increased cavitation formation from water vapor to thereby provide particle diminution.

Contrary to this teaching, according to the present invention homogenization is performed in media other than water (anhydrous) or water reduced, and/or at lower temperatures to reduce or avoid cavitation from water vapor. Surprisingly, a comparable size diminution can be obtained without using destructive implosion shock waves. Contrary, to the general knowledge in the art, Applicants have found that cavitation is not the dominating diminution principle in the present invention. This is further supported by performing homogenization at lower temperatures, e.g. at 0° Celcius or below. A surprisingly similar efficiency in diminution is observed, which is contrary to the general beliefs in the art.

Desai does not address the problems associated with implosion shock waves from water evaporation nor does Desai provide any solutions thereto. For this reason alone, the Section 103 rejection should be withdrawn.

As described correctly by the Examiner, Desai prepares particles of water insoluble drugs. However, particle production does not take place by grinding the drug in its solid state, that means particle diminution is not achieved by subjecting a solid particle to diminution forces. In contrast, Desai dissolves the drug in an organic solvent, an o/w emulsion is prepared consisting of droplets of the organic solvent in water as outer phase. (See page 18, lines 6-15 of Desai) The droplets contain the drug in dissolved form, there is no solid drug particle. The high pressure homogenization process applied by Desai simply reduces the droplet size of the produced emulsion, there is no grinding of solid particles.

In contrast, in the present invention solid particles are emulsified and ground, which is very different from the dissolved solution of Desai. For this reason alone, the Section 103 rejection should be withdrawn.

On page 18, lines 12-14, Desai discloses that an emulsion consisting of nanodroplets results from the high pressure homogenization process. To obtain the particles, the solvent needs to be evaporated to yield particles. (See page 18, lines 20-23). Consequently solid particles are not the result of the homogenization step by Desai, and Desai obtains a nanoemulsion (liquid in liquid).

In contrast, in the present invention, a solid particle suspension is formed and claimed. Thus, the processes are completely different: production of a nanoemulsion by Desai actually representing a particle production by the well known solvent evaporation technology versus processing of a solid particle suspension in the present invention.

In view of the many differences between Desai and the claimed invention, and the unexpected advantages of the claimed invention, withdrawal of the Section 103 rejection is respectfully requested.

In view of all of the rejections of record having been addressed, Applicants submit that the claimed invention is in condition for allowance and Notice to that effect is respectfully requested.

Respectfully submitted,
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